INVOLUNTARY HYPOHYDRATION IN MAN AND ANIMALS: A REVIEW

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INTRODUCTION

After oxygen, water is the most important constituent of many living organisms. In general, the body is able to regulate its water content to meet the vicissitudes of the environment. However, conditions, such as exercise, heat, cold, and altitude, may upset an organism's homeostasis. Various homeostatic mechanisms must then be activated to return the various physiological systems to within their normal operating limits. Failure to do so may cause severe derangement and sometimes the death of the organism.

The voluntary ingestion of water is one of those homeostatic mechanisms. Voluntary drinking in humans is usually stimulated when the body water decreases about 1 percent and the latter is normally regulated to within ±0.22 percent of the body weight (ref. 1). The turn-over of total body water in humans has been estimated at 11 days (ref. 2) and 13.3±2.2 days (ref. 3). Under some circumstances a deficit of body water occurs such that the normal intake mechanisms are not sufficient to insure complete rehydration until some time has passed. This delay in complete rehydration following hypohydration has been termed "voluntary dehydration" by Adolph and others (ref. 4).

The term is misleading in that it leads the reader to assume that the delay in rehydration occurs voluntarily. The opposite is the case. The water-depleted person voluntarily rehydrates completely over a period of time, if water is freely available, and at any moment prior to complete rehydration the deficit of water in the body tissue is involuntary. The term dehydration is also somewhat ambiguous and the term hypohydration, meaning a water deficit, has been suggested in its place (ref. 5). Thus, involuntary hypohydration will refer to a depres-sion in the rate of water intake with the dimensions of volume over time.

The importance of maintaining an adequate water and salt intake while working in hot environments is well known (ref. 6). Men on ad libitum water while working became exhausted much earlier than other men drinking water equal to their sweat loss (ref. 7). Victims of heat prostration, acute anhidrotic heat exhaustion, and plain heat exhaustion are sometimes hypohydrated and often exhibit little or no desire to drink. These heat diseases have been observed in the natural environment by Bannister (ref. 8) and during heat acclimatization studies in the laboratory (ref. 9). Bannister's observations were confirmed experimentally by Sargent and Johnson (ref. 10).

The most important factor limiting work output is the restriction of water, not food (ref. 11). Like food, physical fitness is also of secondary importance to water (ref. 12) and even tough, well acclimatized men will succumb if sufficient water is not available (ref. 13). Sodium chloride (NaCl) is a very important adjunct to water intake, and low salt intakes lead to water abstention (ref. 9), while excessive salt consumption sometimes leads to polyuria because more water is obligated to rid the body of the excess salt. Leithead (ref. 14) concluded that hypohydration reduces sweating and predisposes one to heat stroke and death.

Thus, it can be seen that understanding the mechanism(s) of involuntary hypohydration may help alleviate many of the heat diseases and increase working efficiency in hot environments.

Two excellent volumes (refs. 1 and 15) discuss the entire topic of thirst and drinking, and no attempt will be made to duplicate those

works. The general area of water metabolism has been reviewed elsewhere (refs. 16 through 19). That area and those pertaining to more specific topics, such as the role of water taste receptors (refs. 20 and 21), the physiological and pharmacological control of hunger and thirst (ref. 22), the dispersion of ingested water (ref. 23), and the nervous integration of water and salt metabolism (ref. 24) will not be specifically considered here.

This review is intended to summarize (not exhaustively) the literature pertaining to the delay in rehydration following water loss and other associated factors influencing drinking in man and in other animals. The fact that dogs, cats, burros, and camels do not show as great a degree of involuntary hypohydration as man served to focus attention to the problem. Perhaps, after studying the observations on animals, some insight may be gained concerning the species differences in the lag in water intake and the controlling mechanisms.

INVOLUNTARY HYPOHYDRATION IN MAN

ENVIRONMENTAL PARAMETERS

The phenomenon of involuntary hypohydration was observed many years ago by Hunt (ref. 25) in an experiment on the salt content in sweat following heat exposure. He observed that if the body water was extensively drawn upon, replacement took many hours and restricted drinking might be harmful, an idea contrary to popular opinion in those days. In the early part of the twentieth century it was common for desert travelers to drink very little water during the heat of the day, the deficit being made up during the evening meal. Chase (ref. 26) told of eating a cold supper, drinking about 5 gal of water (probably slightly exaggerated), smoking a pipe, and enjoying a shower bath (of the desert sort by means of his tin drinking cup), and then retiring. This is a perfect description of involuntary hypohydration, although it was not recognized as such.

Vernon and Warner (ref. 27) observed that their subjects always drank less water than they lost by sweating, particularly at high temperatures. Lee and Mulder (ref. 28) studied the effects of a hot moist (dry bulb temperature $=36.1°$ C, wet bulb temperature$=33.3°$ C) and a hot dry (DBT$=43.3°$ C, WBT$=32.2°$ C) environment on male subjects who had had no food or water for 12 hours, noting particularly the reaction to food (four dry crackers, 1 oz butter, and two boiled eggs) and water intake. They emphasized the emotional factors of the subjects during heat exposure and compared thirst feelings between the two environments. The consumption of the standard meal was nearly always followed by an exaggeration of the sense of lassitude, discomfort, and tendency to mental irritability which persons experience in the heat. Drinking water seemed to alleviate the symptoms somewhat. Thirst was much less marked in the wet room than in the dry. The difference in effective temperatures (dry, 35.0° C, and wet, 33.8° C) would indicate that the reason for the difference lies beyond environmental parameters. The possibility that the humidity influences thirst, as the work of Kaufman (ref. 29) suggests, should not be overlooked. After leaving the hot-dry room, the subject's thirst persisted in spite of large draughts of water, indicating that water intake was somewhat depressed during the heat exposure.

The Harvard Desert Expedition to Boulder City, Nevada, in the summer of 1937, provided much information on water balance in the heat. Heat balance was observed to be regulated about 10 times as accurately as water balance over 24-hr periods. Water, always on the deficient side, stayed unbalanced for hours, while heat, always in excess, was being continually lost and was back in balance within 1 hour after cessation of exercise (ref. 30). Fluid intake roughly paralleled the daily maximum temperature and the loss of water in urine and sweat accounted for more than half the total water turnover. It was observed that the various subjects regained their initial water balance, as measured by total body weight, with a precision of 4 to 10 percent of the amount of water exchanged (ref. 31). The times of day at which most water was ingested were with meals and immediately after exercise. During exercise there was little desire to drink, yet during this time 2 to 3 l. of water was lost by evaporation.

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Satisfaction was obtained when half of the fluid deficit had been restored (ref. 31):

Several possible ways of viewing this result suggest themselves. It is possible that, since some solute as well as water was lost, only enough water was required by the subject to render the concentration of the body fluids equal to their previous state. Another doubtful view is that the new content of the stomach or other portions of the alimentary tract is sufficient to allay thirst for the time being. It should be noted that the desire for water is assuaged before much of the water has been absorbed into the blood stream or any other tissue; and even after absorption has occurred only 50 to 70 percent of the water deficit has been replaced within an hour.

Also, pre-exercise ingestion of 1 l. of water was not excreted in the urine and when a dilute NaCl solution was drunk in place of water, the dilute NaCl was retained for several hours before being required for sweat formation.

Dill (ref. 32), commenting on the dry mouth theory of thirst, observed that although he lost 2.8 kg of body weight during an experiment and had a dry mouth, 0.4 kg of water was enough to satisfy his thirst.

Eichna et al. (ref. 12), in a study of performance in various hot, humid environments, found that no subject voluntarily drank enough water to replace the losses in sweat. Furthermore, the feelings of thirst did not develop until considerable water deficits were incurred. On the first day of the study larger water deficits were observed than on succeeding exposures. As the exposure progressed, the voluntary water intake during work increased and more nearly approached the sweat loss. The increase in drinking resulted in smaller water deficits and an increase in performance. It was not clear whether the voluntary increase in water intake was due to the removal of symptoms masking thirst, an increased sensitivity of the thirst mechanism, or merely a learning of the need for water. It was also observed in the same experiments that: (a) the pattern of thirst changed drastically with acclimatization—the water deficit on day 1 averaged 1 l. but was reduced to ½ l. by day 5; and, (b) when large quantities of water were required, there was a phase in which the subjects vomited after which they could drink and retain large amounts of water (ref. 33).

Molnar et al. (ref. 34), after comparing water balances of troops in the California desert and the Florida tropics, observed that in the desert the average 24-hr fluid intakes and sweat outputs were twice as great as in the tropics, but the average urinary volume and urinary salt excretion were the same in both environments. They concluded that water and salt intakes were increased in proportion to the increased losses. Australian cane-cutters, working at 25° south latitude at about 32.2° C (90° F), had a mean fluid intake of 7.01±1.08 l. during the 8-hr work period. Their average weight loss during this period was about 9.1 kg, about 2 kg more than the ingested water (ref. 35).

The effect of climate on food and water intake has been investigated (ref. 36), and water intakes were observed to be essentially the same in the temperature range −20.9° to +15.6° C. Above +15.6° C there was a sharp increase in were increased in proportion to the increased sweating. In the cold and temperate climates there was a relatively constant ratio of water to caloric intake; over 15.6° C this ratio increased markedly (ref. 36). A similar relationship between ambient temperature and water consumption has been observed in infants as well as adults (ref. 37).

People born and raised in arid regions seem to exhibit a much greater resistance to heat and hypohydration than people in Western civilizations. There was some evidence that exposure to heat in infancy may improve heat tolerance in later years (ref. 38). Shaper and Spencer (ref. 39) cited instances where Samburu warriors, in Northern Kenya, were sufficiently conditioned at most times to walk 30 miles or more a day in the hot sun with little chance of finding water more than once. There are recorded instances where warriors traveled 70 miles a day under the same conditions.

Burns (ref. 40) investigated the diet, water intake, and urine variables of the Ababda tribespeople living near the Marsa Alam well in the Eastern Desert of Egypt near the Red Sea. The urine specific gravities of 71 percent of the people tested were in the 1.020 to 1.030 range. The specific gravity did not seem to be influenced by the time since the last drink of water.

Two of the subjects had had no water for 12 hours—a remarkable period of deprivation in the desert—and their urine specific gravities were still in the 1.020 to 1.030 range. Americans, serving as control subjects, had urine specific gravities ranging from 1.030 to 1.041 despite a liberal intake of water. The urine sodium, osmolarity, and total electrolytes were essentially the same in the control and native subjects, while nitrogen and potassium were considerably higher in the controls. The natives, then, when confronted with a diminished water intake, did not exhibit an increased urine specific gravity. The urine of water-depleted natives had lower specific gravities than that of controls drinking ad libitum. It is possible that the Americans were undergoing some degree of hypohydration. A more likely explanation is that the natives have adapted to the lack of water in much the same fashion as the desert travelers described by Chase (ref. 26).

Involuntary hypohydration was evident in five resting men in flying suits undergoing thermal stresses of 46° C (115° F) and 54° C (130° F) (ref. 29). Two levels of water vapor pressure, 10 and 20 mm Hg, were employed at each temperature. All five subjects completed 8 hours at 46° C, 10 mm Hg. The hypohydration was approximately 3.5 percent of their body weight. In the other three experiments of 46–20, 54–10, and 54–20, the mean tolerance times were 4.4, 4.1, and 2.2 hours, respectively. The final hypohydrations were about 3 percent in each of the three experiments and the amount of heat stored per kilogram of body weight was essentially the same in each case. Thus, heat tolerance seems to be related to the time it takes to become water depleted to about 3 percent of the body weight. The final rectal temperatures were about 38.3° C (101° F) and heart rates were about 130 beats per min, neither of which would necessarily be incapacitating. The food intake was completely inhibited in the 54–20 experiment and the water intake nearly so (39 ml/hr). During the other three experiments the food consumed averaged 180 g and the average water consumption was about 120 ml/hr.

This negative water balance in subjects per-forming in very hot environments is usually the rule rather than the exception (ref. 41). It appears that the lower limit of environmental temperature associated with this inhibition of drinking is 49° C. Kaufman observed the inhibition during one of his 54.4° C (130° F) experiments but in neither of the 46° C (115° F) experiments. Greenleaf and Sargent (ref. 42) observed it in heat-acclimatized subjects previously hypohydrated about 5 percent of the body weight walking at 6.4 km/hr at 49° C. A heat-acclimatized man with a water debt of 3 to 3.5 l. responded to a heat-work stress much like a normohydrated unacclimatized man (ref. 43). It is clear that parameters other than temperature alone mitigate this inhibition of drinking. The highest water consumption in Kaufman's study (225 ml/hr) occurred during the 54–10 experiment. Various combinations of temperature (49° or 24° C), exercise (6.4 km/hr or resting), and previous hydration (5 percent of body weight loss or ad libitum) resulted in an inhibition of water intake, roughly proportional to the degree of the total stress imposed (ref. 42). Thus, such factors as heat, humidity, exercise, and previous hypohydration may not grossly affect voluntary water consumption when encountered singly, but if taken in combination their effects may be considered additive and result in increasing inhibition of drinking.

Involuntary hypohydration has also been observed in subarctic simulated survival situations (ref. 44). A diminished voluntary intake during 5 days of starvation was the principal cause of water deficits because the urine volumes were not increased above the control volumes. The days on which the involuntary hypohydration was most severe were also the days of greatest sodium excretion. If greater amounts of water were taken during the periods of increased sodium excretion, the urine volumes were correspondingly increased and the final net water deficits were the same as the others. In 5 days the subjects lost 15 percent of their extracellular fluid volume; it was an isotonic fluid loss. These observations strengthen the volume receptor theory of thirst (ref. 1).

SALT AND FOOD INTAKE

Arden (ref. 45) observed the reactions of his subjects after they drank 200 ml of a 10-percent NaCl solution. Thirst was evident after 30 min and the mouth was becoming dry by the end of an hour. Saliva secretion ceased entirely in 2 hours, the mouth was parched and thirst was excessive. At 7 hr after the salt was taken, thirst had almost disappeared and the mouth was moist, even though there was still a considerable amount of excess salt in the body. When 15 g of potassium was taken, there was no thirst. Arden suggested that thirst might be governed by the sodium ion alone. Subsequent studies have not substantiated this hypothesis (refs. 46 through 48).

Subjects undergoing starvation and offered water ad libitum following hypohydration retained only part of the water ingested even though considerable deficits were present. However, enough was retained to dilute the serum sodium slightly below its initial concentration so that the body water became hypotonic (ref. 49).

Baker, Plough, and Allen (ref. 46) presented evidence that voluntary water intake was roughly proportional to sodium chloride intakes of 393 (11.8 g) and 530 (15.8 g) milliosmols per liter (mOsm/l.). With salt intakes of 803 and 1104 mOsm/l., the water intake of 4 out of 6 subjects was severely diminished. The fact that simple water deprivation delays rehydration throws doubt on the hypothesis put forth by Smith (ref. 50) that rehydration follows salt replacement. In simple, uncomplicated hypohydration the salt content of the body would be normal or even slightly elevated (ref. 51); this elevation should stimulate drinking and normal hydration should occur rapidly. This does not always happen (ref. 46). Thus, involuntary hypohydration occurs with either an elevated or depressed serum salt concentration. In an experiment to test the effect of salt replacement in reducing involuntary hypohydration, there was an increase in fluid intake and a decrease in urinary volume but they were not considered statistically significant (ref. 52). However, Coller and Maddock (ref. 53) observed a patient who lost about 4 kg of water over 4 days and drank 6 l. of water during the first recovery day.

McClendon (ref. 54), in experiments on normal men, observed that drinking water while fasting resulted in small changes in blood volume; all of the ingested water was excreted within a few hours. When 400 g of glucose was taken with 2400 ml of water, there was a marked increase in blood volume due to water retention and an increase in body weight of about 1 kg.

The effect of administering saline solutions for improving body water retention was confirmed by Lee and Boissard (ref. 55) and Lee et al. (ref. 56). When the salt intake was low (6 g/day), men working in the heat and drinking water ad libitum lost more than twice as much weight, drank less water, and sweated less than those on the moderate salt intake (15 g/day). The low salt group ended the first 24 hr with hypohydrations of 2.5 percent of the body weight compared to a 0.77 percent deficit in the moderate salt group. Dill (ref. 32) and Nadal, Pedersen, and Maddock (ref. 57) also observed the failure of the thirst mechanism following a low salt intake.

When 81 mine workers were queried concerning fatigue, sweating, headaches, and cramps, 11 of the workers denied drinking any water during working hours. Several miners mentioned that they consumed liberal amounts of salt a mealtime (ref. 58). Ladell (ref. 59) thoroughly investigated the effects of water and salt intake on performance in the heat, and one important conclusion was that subjective effects were more marked than objective effects in subjects on various salt and water regimes.

A slightly larger mean involuntary hypohydration was observed in Indian subjects eating 19 g of NaCl per day than in those eating 38 g during 8 hr of work in the heat for 6 consecutive days (ref. 48). It was concluded that the high salt intake was unnecessary.

A relatively constant ratio of food to water intake has been observed in humans. After 4 days of refeeding, following acute starvation with hard work, the plasma and thiocyanate space volumes exceeded the control values by 12 and 5 percent, respectively. This was evi-

dence that the recovery weight was due, in large part, to an increase in body fluids. Forty percent of the weight gained was accounted for by an increase of 2.4 l. in the thiocyanate space (ref. 60). Competitive lumberjacks reduced a good portion of their involuntary hypohydration by drinking special mixtures of sugar and milk or other heavily sugared drinks during the work period. There was an average weight loss of 1.2±1.5 kg during the competition and that was largely made up at mealtime (ref. 61).

SWEATING AND ELECTROLYTES

When the magnitude of involuntary hypohydration is discussed, a comparison is usually made between the sweat loss and the time it takes to drink an equivalent amount of water. Since the blood chloride remains constant or decreases slightly following heavy sweating, and the concentration of chloride in sweat is usually less than in serum, the serum chloride should increase following sweating because there is a relatively greater loss of water than chloride from the serum. Itoh (ref. 62) studied the effect of walking in the heat, without eating or drinking, on variations in sweat and urine chloride. Water was given ad libitum following the exercise, and a marked lag in rehydration was noted. Itoh also emphasized that thirst varied considerably between individuals. Johnson, Pitts, and Consolazio (ref. 63) investigated the effect of ingested water on sweat chloride and concluded that: (a) sweat chloride increased during work, (b) serum chloride increased when water was withheld and decreased after drinking, and (c) there was no apparent correlation between sweat and serum chlorides. They also found that sweat chloride decreased more after ingestion of saline solution than after an equal volume of water.

During a steady state of water intake, the ratio of the rate of chloride excretion to the rate of excess water excretion is equal to the normal plasma concentration. When renal excretion is considered, the regulation of the plasma chloride concentration takes precedence over the regulation of body volume (ref. 64). Thus, the body will hypohydrate itself to maintain a constant plasma chloride concentration. Smith

(ref. 50) mentioned that after sweating, man quenched his thirst with a little water, and the total volume of body fluid was restored over a period of hours or days as the lost salt was replenished through the dietary intake.

Another phenomenon associated with drinking, and possibly with the lack of it, is the outburst of sweating that often follows water consumption. Lee and Mulder (ref. 28) made the following observations on the reaction: (1) The water must be swallowed; rinsing out the mouth is ineffective. (2) Isotonic saline produces the same effect as water. (3) The onset of sweating begins within 3 min after drinking. (4) The outburst of sweating begins before there is any noticeable dilution of the blood. (5) The degree of response is roughly proportional to the amount of water ingested. (6) If food is taken with the water, the response is delayed and of lesser magnitude.

Saito (ref. 65) observed the outburst of sweating in eight men and one woman after drinking water at 5°, 36.5°, and 50° C following 2 hr of exercise or following a rest period. Sweating began immediately after drinking the 50° C water and stopped within 15 to 25 min. If the subjects were sweating when the 5° C water was taken, a sudden inhibition in the sweating occurred which lasted about 10 min. The sweating returned gradually during the ensuing 10 min, but there was no compensatory increase. The effects of drinking the 36.5° C water varied with the sweating condition of the subject. Nonsweating subjects showed no change but sweating subjects exhibited a transitory outburst. If the 36.5° C water was drunk following muscular exercise, a profuse outburst occurred which lasted about 30 min. The outburst following the 50° C water consumption and the inhibition after the 5° C water consumption were attributed to a reflex mechanism while the effects of the 36.5° C water consumption were ascribed to an increase in blood water.

The state of previous hydration has also been suggested as a controlling factor in this sweating phenomenon. After drinking 300 ml of 35° C water following intolerable thirst, the subject felt hot, was flushed, and sweating was increased by 3 g/min and was maintained for 20

min. Carbonated water caused an even stronger reaction. If the subject was not thirsty, drinking caused a much milder sweating reaction (ref. 66). Further, it was observed that ingestion of 1 l. of 0.9 percent NaCl solution inhibited sweating while subjects were in a steam bath but promoted sweating in the subjects at normal room temperature. Also, normal sweating was increased and heavy sweating was inhibited by normal saline, while tap water had no effect upon normal sweating but greatly increased an already increased sweat secretion (ref. 67). This latter finding was confirmed by Marschak and Klaus (ref. 68).

It is entirely possible that the pharyngeal-satiating component of drinking was responsible for the outburst of sweating following drinking. If the shut-off mechanism for drinking were controlled by the amount of water passing the pharynx, it would be much easier to explain involuntary hypohydration. Thus, drinking would cease when a measured amount of water was swallowed. The setting of the pharyngeal "flow-meter" might then be controlled by such things as blood osmolarity, gastric distension, the volume of body water, etc. Whether the outburst of sweating following drinking is related to involuntary hypohydration or is just a by-product of drinking remains to be elucidated.

Absence of thirst has been observed in patients exhibiting hypernatremia and hyperosmolality of the body fluids (refs. 69 and 70). However, the latter case was complicated by a cerebral lesion. Avioli, Earley, and Kashima (ref. 71) described a case in which 2.5-percent saline was administered to an alert, ambulatory patient. The serum osmolality was raised to 335 mOsm/l. and the sodium to 179 meq/l. and no thirst or other discomfort was present. Diabetes insipidus was also present, which would tend to increase thirst. Some time later the patient died. Postmortem study revealed widespread hypothalamic destruction. Thus, thirst accompanying serum hyperosmolality and hypernatremia seems to depend upon hypothalamic integrity.

There is no doubt that one of the principal stimuli for thirst is the rise in serum osmolal concentration. Other effective stimuli include extracellular volume changes, oral sensations, conditioned reflexes, and habit patterns (ref. 72).

HYPOHYDRATION

Simple water deprivation can also lead to involuntary hypohydration. Nadal, Pedersen, and Maddock (ref. 57) investigated the two types of water depletion, primary salt loss and water loss not accompanied by a corresponding loss of salt, and found that thirst was not present in both types. It was present only in the water-deprivation type and was often completely absent in the extracellular or salt-loss type.

It was interesting to note that a change in hydration up to 2 percent of the body weight could occur without a corresponding change in salt or solid content. Rothstein, Adolph, and Wills (ref. 52) observed that "voluntary dehydrations" of 2 to 3 percent were not uncommon in field tests. In some cases the failure to voluntarily maintain water balance resulted in considerable hypohydration, even approaching dehydration exhaustion. These levels of water loss led to fatigue, apathy, low morale, unwillingness and inability to undertake strenuous activity, and generalized discomfort. The implication here was that perhaps water intake was regulated to within 2 percent of what it theoretically should be if the salt concentration were the basis for measurement.

In another study concerning only water depletion, Black, McCance, and Young (ref. 51) investigated two subjects who abstained from water for 3 and 4 days, respectively. They ate a dry diet adequate in protein, calories, and salt. Thirst was never unbearable, but the third day their voices became husky and they had difficulty swallowing. By the fourth day there was a suggestion of cyanosis around their lips. The appearance of ill-being vanished within a few hours once the subjects began to drink. Thus the symptoms of the hypohydration were removed long before restoration of the depleted body water was completed. "Many of the subjects lost all their desire to drink as soon as the first pint of fluid had been taken" (ref. 51).

Greenleaf and Sargent (ref. 42) also observed these same phenomena. It appeared that the body adapted in some fashion to the chronic water depletion. It has been observed that men drank less of the water they had lost after the second period of hypohydration than after the first (ref. 52).

Rothstein, Adolph, and Wills (ref. 52) named and defined "voluntary dehydration" and studied it in desert troops. Their work may be summarized as follows: (1) Voluntary dehydration occurs between meals and the deficit, if it is not too large, is made up at mealtime. (2) The voluntary dehydration measured in men marching, in tank crews, in ground crews, and in pilots was between 2 and 5 percent of the body weight. (3) Voluntary dehydration can be reduced if no meals are missed, if sufficient pure water is available, and if ample leisure is provided between meals for the men to quench their thirst. (4) Unnecessary activity should be eliminated because sweating leads to a greater voluntary dehydration. (5) Men should be encouraged to drink more water than they feel they want. (6) The greater the loss of body water, the greater the length of time needed to remove the deficit. It was suggested that hypohydration might become more insidious as the day passes if the body adapted to the water deficit.

Wills (ref. 73) suggested that the capacity of the stomach prevented rapid rehydration. In 29 paired tests, within 2 hr after completion of the marches, those who had marched without any water reduced their deficits of body weight equal to those drinking ad libitum during the marches. The men drank rapidly during the first 15 to 20 min of the rest period. Their total loss of water was replaced if it was not greater than 2 percent of the initial body weight. Any residual deficits were made up with meals. Cool water was the most preferred drink. Flavored drinks, warm water, and salted water were less palatable.

Sohar, Kaly, and Adar (ref. 74) and Sohar, Gilat, Tennenbaum, and Nir (ref. 75) marched 19 physically fit young men from Eilat, in the south of Israel, to Metulla in the north, a distance of 370 miles, in 24 days (including 3 days of rest) during August 1959. The men averaged about 17 miles per day carrying a 35-lb load. Involuntary hypohydration could be reduced by providing a cold, sweetened, fruit-flavored drink, as well as cool water. Beer, milk, and carbonated beverages were not suitable for drinking in large quantities. It was decided that the temperature of the drinks should be 10° to 12.8° C (50° to 55° F). Involuntary hypohydration was further reduced by providing rest periods of 20 to 30 min after having the men march 2 to 3 hr. These rest periods allowed more time for drinking than the usual 10-min rest per hour employed by the military. Starkenstein (ref. 67) suggested that not only the salt content, but also the pH of the drinking water was an important consideration when considering a rehydration fluid. He showed that (1) the degree of acidity of drinking water had an inverse relationship to the body's ability to retain it; and (2) the pH does not inhibit the retention ability of saline. He inferred that the best rehydration drink would contain a salt concentration slightly lower than 0.9 percent and have a pH about 6.0. These results were essentially confirmed by Ilzhöfer and Brack (ref. 76) under exercise conditions.

Leithead and Pallister (ref. 77) and Leithead (ref. 78) studied the relation between hypohydration and sweating during the heat acclimatization of 18 fit men of the Royal Air Force. The daily fluid intake of their subjects averaged 6 to 7 pints per man, not enough to maintain circulatory stability, nor a satisfactory urine output. The water supply was located across the compound in the mess-hall; most of the men preferred to stay in their barracks and endure the thirst, thus accentuating their water deficit. Further, the authors concluded that hypohydration caused a reduction in sweating, both on the basis of their own data and after a critical review of the literature. Thus, involuntary hypohydration possibly takes on another dimension. Ellis et al. (ref. 79) and Ellis, Ferres, and Lind (ref. 80) obtained results similar to Leithead and Pallister in that increased consumption of water produced more sweat and less water produced less sweat. The

greater the amount of cool water consumed, the slower the rise in the rectal temperature and the longer time resting subjects could endure an environment of nearly saturated air at 37.4° C (99.4° F).

Yoshimura et al. (ref. 81) had a unique opportunity to study a Buddhist bishop, Soken Enami, 46 years old, who underwent complete food and water deprivation for a period of 8 days during religious rites. The rites were divided into three parts. The first lasted 100 days during which time the priest ate vegetable food composed mainly of potato, buckwheat flour, and other vegetables except cereals. On the first day of the starvation period which followed the 100-day dietary period, he ate 2 meals, morning and noon. Then complete starvation commenced and continued to the ninth day. During this period he performed his religious functions and prayed before a large fire for about 90 min/day. The remaining time was spent resting and sleeping in his bed. The priest rinsed his mouth with water when severe thirst occurred, but all the water was spewed out. The third part of the rites, the rehabilitation period, commenced on the morning of the ninth day. First he drank a cup of water containing wood from *Magnolia ovovata*, then some "amazake" (a Japanese hot drink consisting of steamed waxy rice granules cultured with *Aspergillus oryzae;* this was added to a rice gruel and heated at 60° C for several hours). Thus, he gradually increased his food and drink and was rehabilitated.

Conspicuously absent from the report was the mention of the priest gorging himself with water on the ninth day. The self-discipline of such a person would have precluded such a display; it is entirely possible that he simply was not very thirsty after his first few drinks. There was a gradual increase in the water and food consumption during the recovery period. The calmness and self-control of Bishop Enami was in marked contrast to the reactions of Captain Nolan's men who were without water for 3 days in the Texas desert (ref. 82). They could not refrain from gulping down water which was promptly vomited. The same thing occurred when they tried to eat dry food. It is clear that mental and physical quietude is essential for adaptation to total starvation and hypohydration. It is recognized that the two environmental conditions were not directly comparable; the desert imposed a much greater stress on the body water than the environment in the Buddhist's temple. One cannot help wondering what effect a real survival situation, as compared with a controlled situation offering no danger, has on the sensation of thirst and the physiological reactions during rehydration.

GASTROINTESTINAL FACTORS

The gastrointestinal system is important in the control of water balance. All ingested water must be absorbed by this system before entering the body tissue. Salivary secretions (ref. 83), pharyngeal movements (ref. 84), and stomach distension (ref. 73) have all been implicated in the thirst activation and satiation mechanisms.

Wilks (ref. 85) cited three patients who had intense thirst as a result of displacement of the stomach due to a diaphragmatic hernia. The patients filled their stomachs with water, and they drank still more. Exercise also influences the emptying time of the stomach. The average emptying time was 37 min longer resting than walking (ref. 86); running slowly for 2 to 3 miles retarded the secretion of gastric juice and decreased the rate of emptying, whereas walking increased emptying; walking with a friend and talking further hastened emptying, emphasizing the importance of emotional factors in digestion (ref. 87). The amount of exercise needed to delay digestion varied with the physical fitness of the subject, and it was concluded that the retardation in digestion was proportional to the amount of distress caused by the exercise (ref. 88). Compared with water, an equal volume of 50-percent dextrose solution did not change the emptying time of the stomach at rest or after mild exercise (ref. 89).

Gastric emptying time was faster at 48.9° C (120° F) than at 25° C (77° F) in resting men and was not changed if the subjects exercised at the higher temperature (ref. 90). Following ice water ingestion, the average emptying time of the stomach was delayed 30 to 45

min (ref. 91). Relatively large quantities of water (1000 ml) taken with meals had no significant effect on gastric emptying time (ref. 92).

Failure to absorb water fast enough from the alimentary tract was postulated as a factor causing involuntary hypohydration in man (ref. 93). The average time for absorption of deuterium oxide (D_2O) from the stomach of healthy, resting subjects was 34.2 min for 67 percent and 54.2 min for 95 percent of the administered dose; from the small intestine the average time was 3.7 and 10.0 min for 67 and 90 percent, respectively (ref. 94). This differential rate of absorption was also observed using varying concentrations of NaCl. Hypertonic saline failed to influence the rate of absorption of water in the stomach, but significantly retarded absorption in the small intestine (ref. 95). Deuterium oxide passed from the small intestine into the blood stream about twice as fast as radiosodium; both were absorbed rapidly—67 percent of the D_2O in 7 min and the same amount of radiosodium in 10 min (ref. 96). The rate of absorption of both D_2O and radiosodium was significantly reduced following the intravenous injection of methantheline bromide (Banthine). The reduced absorption was attributed to a diminution of the absorbing surface to which the isotopes were exposed due to the hypomotility produced by the drug (ref. 97). Water is also exchanged in the large intestine. The mean flux out of the lumen was approximately 7.8 ml/min and the flux into the lumen was 6.0 ml/min. The net flux into the circulation was 1.8 ml of water, 0.28 meq of sodium, and 0.39 meq of chloride per minute during constant perfusion of the colon (ref. 98).

Salivary flow is definitely related to thirst and drinking (refs. 83 and 99) but its relative importance to the total mechanism has not been established. However, persons with congenital absence of salivary glands experienced thirst, did not have an increased water consumption, and seemed to have a normal water and salt metabolism (refs. 100 and 101). These findings would indicate that the salivary glands are not the most important mechanism of thirst, but

they cannot be dismissed entirely because compensatory mechanisms might have come into play in the subject with no glands. Intravenous injection of 5-percent NaCl was associated with a reduction in salivary flow and severe thirst; the plasma and extracellular volumes increased 5 to 10 percent. Drinking 400 to 600 ml of water 20 to 30 min prior to the salt injection alleviated the thirst and reduction in salivary flow caused by the salt injection even though the same increase in the plasma and extracellular volumes was observed (ref. 102). These observations suggest that osmotic changes are not the only factors influencing thirst and that volume changes must also be considered.

Part of the satiation mechanism might be activated by muscular activity in the esophagus. Hypohydrating men exhibited an increasing activity of the esophagus that disappeared after they swallowed a few times (ref. 84).

RECAPITULATION

Thus, many parameters, heat, cold, exercise, food, sweating, water depletion, electrolyte changes, and gastrointestinal factors, are seen to be related to drinking and involuntary hypohydration.

1. Involuntary hypohydration usually occurs after a water loss of about 2 percent of the body weight. The more water lost, the longer the time needed for complete replacement.

2. Drinking is greatest immediately after exercise rather than during exercise; drinking is also increased during rest periods, especially at mealtime. Cool water is usually preferred to warm water; citrus fruit drinks show varying degrees of acceptance. Salt water, milk, alcoholic and carbonated drinks are not well tolerated in the heat. However, Finnish lumberjacks drink sugared milk during their work.

3. Drinking is closely related to food consumption. Following starvation, water intake parallels food intake. Most of the liquid consumed during fasting is excreted, probably due to sodium depletion. Following hypohydration and starvation, the quantity of water retained is just enough to make the body water slightly hypotonic. If glucose is added to the

water, more water is retained, principally in the extracellular fluid.

4. There may be some adaptation to water loss—less water is consumed in successive periods of hypohydration.

5. The climatic effect on the increase in water consumption is due to increased water loss in the heat. Involuntary hypohydration is usually observed after exercise in the heat. Water intake is roughly proportional to the daily maximum temperature above 15.6° C. Acclimatization to heat seems to increase the water intake. At the same effective temperature, thirst is less, and involuntary hypohydration is less in a hot-wet environment than in a hot-dry environment.

6. Thirst following saline intake subsides after about 8 hr although the excess salt is retained in the body. Intravenous injection of a 5-percent NaCl solution decreases salivary flow and increases thirst; preinjected water diminished this reaction. Saline is retained longer in the body than plain water. Involuntary hypohydration occurs following both loss of salt and not water and loss of water but not salt. If both salt and water are lost simultaneously, replacing the salt does not alleviate involuntary hypohydration very much. Water intake follows salt intake up to 15 g/day; higher salt intakes can depress drinking. Water and salt intake increase, approximately, in proportion to the losses, but the rate of rehydration is constant and independent of the level of hypohydration attained.

7. Following potassium ingestion, thirst is not increased as it is following sodium ingestion. Serum chloride decreases after drinking. The regulation of plasma chloride takes precedence over the regulation of body volume.

8. Hyperosmotic serum is not associated with thirst if there is specific hypothalamic destruction, and hypothalamic integrity seems to be necessary for the manifestation of thirst.

9. Water gulped in large drafts seems more satisfying than small drafts. Large amounts of water drunk rapidly may cause vomiting. However, once the initial vomiting is over, large drafts can then be consumed and retained.

10. The capacity of the stomach may cause involuntary hypohydration. Hard exercise and emotional conditions delay gastric emptying; mild exercise facilitates emptying. The higher the level of physical fitness, the greater is the intensity of the exercise needed to delay gastric emptying. Gastric emptying is faster at 48.9° C (120° F) than at 25° C (77° F). Ice water delays emptying. Large quantities of water taken with meals have no delaying effect.

11. Water is absorbed much faster from the small intestine than from the stomach. In the small intestine, water is absorbed twice as fast as sodium. Hypertonic saline has no effect on the absorption time in the stomach, but it significantly retards absorption in the small intestine. Decreased motility of the small intestine also delays absorption.

INVOLUNTARY HYPOHYDRATION IN ANIMALS

DOGS

This material will be presented and discussed under the following headings: the drinking pattern, neuroendocrine factors, electrolyte variations, hemorrhage, heat and hypohydration, exercise, gastrointestinal factors, and food intake, followed by a recapitulation.

Drinking Pattern

Drinking rarely occurred before the dogs lost 0.5 percent of their body weight (ref. 103). A deficiency of body water appeared to be the chief factor in inducing drinking, not the time that lapsed during its loss. The amount of water drunk was accurately proportioned to the water deficit at each draft even though there was little absorption before drinking ceased. The authors presented the concept that the state of hydration was continually oscillating about the point of water balance. The amplitude of this oscillation was quite constant and the period varied with the rates of water exchange, the latter being influenced by changes in the rates of catabolism or sudden additions of food.

Fistulous dogs, hypohydrated at least 2 percent of their body weight, sham-drank enough water to equal the deficits every 40 min (ref. 104). The velocity of drinking in fistulous dogs was nearly constant during the periods of continuous drinking and the intervals between drinks were characteristic of each animal (ref. 105). Further, normal dogs, when deprived of water, satisfied their thirst with a single draft in less than 5 min and exceeded the water deficit by less than 17 percent—that is, they always overhydrated.

Bellows (ref. 106) confirmed Adolph's findings (refs. 104 and 105) concerning the time factors and individual drinking patterns in fistulous, hypohydrated dogs. Two additional factors were brought out concerning the satisfaction of thirst: an excessive amount of water passing through the mouth and pharynx conferred immediate but temporary satisfaction, and repetitious drinking and swallowing was inhibited when the water entered the gut. It was postulated that permanent satisfaction was conferred by processes operating lower in the gut (ref. 106).

Neuroendocrine Factors

Normal dogs and those with diabetes insipidus showed no alteration in their drinking responses following anesthesia of the pharynx, and resection of the olfactory, trigeminal, and glossopharyngeal nerves (ref. 107). In addition, the effects of vagotomy and sympathectomy on drinking were investigated by Towbin (ref. 108) to define the role of the gastric distention factor (ref. 109) in controlling water intake. Vagotomy caused the dogs to increase the volume of their drinks. This would be expected if the vagi carried afferent distention stimuli. If the stimulus to stop drinking were abolished, the shutoff mechanism would tend to be sluggish and the dog would tend to overshoot his usual water intake. Thoracic sympathectomy had the opposite effect of vagotomy. During the control periods it was observed that the dogs tended to drink the same amount of water with each draft. The volume was not grossly affected by environmental temperature, total food or water intake, or small changes in body weight. The total water consumption per day was controlled by varying the number of drinks.

Thyroid feeding (16 to 80 g/day) increased fluid intake five to eight times that of the control periods, and, in most instances, the drinking was greater (by 2 l./wk) with isotonic saline than with water (ref. 110).

Following NaCl injection, the only way pitressin affected sham-drinking was to delay its onset by 10 to 20 min (ref. 106). Barker, Adolph, and Keller (ref. 111) concluded that hydropenia (5 percent) and hyperchloria (10 mM NaCl/kg) did not affect drinking in the same manner: (a) Drinking after hydropenia was enhanced by pitressin, drinking after hyperchloria was not; neurohypophyseal lesions acted like pitressin. (b) Pitressin alone was not a stimulus to drinking. (c) The stalk of the hypophysis was not the only pathway of gastric influence because the overdrinking dog was still subject to inhibition from gastric filling (ref. 111). Their dogs with lesions presented an abnormality of drinking that was independent of urinary excretion.

Ablation of the ventral anterior hypothalamus led to polydipsia, but if the lesions were extended dorsolaterally, adipsia resulted. After the dogs became severely water depleted, they refused plain water. If the water was baited slightly with meat juice or milk, the animals drank ravenously; they perceived the baited water as food but not as water (ref. 112). This latter finding was confirmed by Anderson and McCann (ref. 113) who also found no correlation between the absence of drinking and diabetes insipidus. The degree of depressed drinking was proportional to the size of the hypothalamic lesion. These two studies further support the role of the hypothalamus in the control of water intake.

Higher brain structures also exert an influence on water intake. Amphetamine (1 mg/kg of body weight) will inhibit the urge to eat and drink in the normal dog after an intravenous injection of 20 ml of a 20-percent NaCl solution. This was no longer the case in three out of five dogs after "prefrontal lobotomy." The lobotomy alone did not reduce normal drinking or the amount of water consumed after injecting hypertonic saline (ref. 114).

Electrolyte Variations

Much work has been done on electrolyte variations and water intake. Darrow and Yannet (ref. 115), studying dogs, rabbits, and monkeys, described two phenomena which have been incorporated into the osmometric theory of thirst. The first involved the loss of extracellular electrolyte with little change in total body water. This condition induced symptoms and signs of hypohydration, although there was no water loss. It was postulated that some of the extracellular water shifted into body cells. In the second condition there was an increase in extracellular electrolyte with little change in total body water. Here, only thirst was evident because water had shifted from body cells into the extracellular spaces. These, and similar observations on man by other investigators, led to the idea that the thirst mechanism could be explained by the degree of cellular hydration (osmometric theory).

After the hypohydrated state had been prolonged for 7 days, the following additional observations were made: The signs and symptoms of hypohydration persisted until the NaCl deficit was replaced. Dogs with large salt deficits refused to eat; other dogs in similar condition vomited if food was in the stomach when the electrolytes were removed. Oliguria was present for about 24 hr, and no water was drunk during that time; when urine flow was re-established, water intake and urine output approximated that of a starvation condition. The signs and symptoms of hypohydration were unaffected, in spite of the comparatively normal fluid intake.

It was concluded that:
1. Hypohydration is a phenomenon which does not involve body water alone.
2. Diuresis does not develop under certain conditions characterized by a relative excess of water in relation to electrolyte.
3. Thirst is not an obligatory accompaniment of hypohydration.
4. Water intake and urine output may be normal in the presence of hypohydration (ref. 116).

Gilman (ref. 117) advanced the osmometric concept of thirst one step further. After inject-

ing 2.5 ml/kg of either 20-percent NaCl or 40-percent urea, he found that despite an identical rise in blood osmotic pressure, the fluid intake 15 min after sodium chloride administration was 32 ml/kg, over twice that following urea. After NaCl, the blood osmotic pressure returned to normal within an hour; after urea, the voluntary water intake was so low that the osmotic pressure remained elevated for some time. Gilman concluded that cellular hypohydration, as opposed to an increase in cellular osmotic pressure per se, is the stimulus of true thirst.

Bellows (ref. 106) extended Gilman's observations. After NaCl injection, sham-drinking started immediately and reached a maximum in 10 min; after urea, the instigation of sham-drinking was delayed 10 to 15 min. Thus, intravenous injections of NaCl led to immediate drinking of a sufficient quantity of water to lower the blood osmotic pressure to normal within 1 hr, while injected urea delayed the onset of drinking much smaller quantities of water so that the osmotic pressure remained elevated for an extended period of time. Since the NaCl and urea were isosmolar solutions, elevation of osmotic pressure was not *the* mechanism controlling water intake.

The type of osmol seemed to be important as well. Remington, Parkins, and Hays (ref. 118) stressed the importance, not only of the extracellular electrolyte levels, but also the intracellular *volume*. Dogs maintained on a salt-free diet did not drink while their intracellular fluid volumes were maintained above normal by intraperitoneal glucose injections. Drinking returned when the intracellular volumes were reduced toward normal. Intake then rose to polydipsic levels, but extracellular volumes were not restored to the pre-experimental levels until sodium chloride was given.

Some additional observations that tended to discredit the osmometric theory but extended our knowledge of thirst and drinking were put forth by Holmes and Gregersen (refs. 119 and 120) and Holmes and Cizek (ref. 121). In the course of experiments with intravenous injections of hypertonic solutions in dogs, Holmes and his colleagues observed that: (1) With equal

doses of salt, there were large individual variations in the duration of drinking and the amount of water ingested. (2) Each dog had his own characteristic response pattern that was consistent from day to day. (3) The volume of water ingested was not related to the amount of water necessary to dilute the injected salt to isotonicity as suggested by Gilman (ref. 117). (4) If water were placed in the stomach 30 min before the test, drinking did not occur. (5) If water were placed in the stomach at the time of the test, drinking did occur; this was probably due to absorption. (6) If the initially ingested water were withdrawn through a gastric fistula, drinking began again within 5 min. (7) Denervation of the stomach did not alter the drinking response. (8) Pitressin given before the salt injection delayed the onset of drinking; this confirmed Bellows' observations (ref. 106). (9) Sorbitol and sucrose were as effective as NaCl in eliciting drinking; glucose was much less effective. (10) The drinking response was the same whether the dog was given water at once or at the end of 1 to 4 hr. (11) The relation between the increase in serum sodium concentration and the water intake may be different in different dogs. The drinking response to a test solution, composed of 50-percent glucose combined with 10-percent NaCl, was the same as that obtained with 10-percent NaCl alone. Osmotically equivalent solutions of sodium sulfate, sodium acetate, and sodium chloride were administered to evaluate the chloride ion as a stimulus. The drinking responses to the three solutions were essentially the same. After the injection of 20-percent NaCl, three dogs each drank twice as much of an 0.8-percent saline solution as of plain water. The saline drinking was completed long before the ingested fluid produced measurable changes in the concentration of the serum electrolytes. It can be concluded that thirst is not specifically regulated by the blood sodium or chloride concentrations.

The observation that some dogs showed decreased drinking following extracellular electrolyte depletion by peritoneal dialysis was probably due to the general depression following such procedures and not to cellular overhydration (ref. 122). Following salt loading,

dogs differed in their excretion patterns as well as in their water intakes. Two types of regulating mechanisms were observed: maximal internal regulators corrected any imposed imbalances mainly by drinking; and minimal internal regulators excreted large volumes of dilute urine. The kidneys do not serve as thirst receptors because dogs both with and without kidneys (ref. 123) will drink the same amount of water after a salt load.

Following injections of hypertonic saline, procaine had little effect on water intake and bilateral section of the vagosympathetic trunk in the neck and complete sympathectomy did not influence the latent period or volume drunk (ref. 124). The volume and injection speed of the hypertonic saline influenced the drinking responses. Smaller doses injected over a longer period of time diminished the water intake and the responses became more consistent (ref. 125).

Holmes and Montgomery (ref. 126) postulated a mechanism for the satiation of thirst in dogs:

Passage of fluid through the mouth and upper esophagus temporarily relieves thirst for approximately 10–20 minutes. The presence of fluids in the stomach satisfies thirst and inhibits drinking for a period starting after about 20 minutes and lasting 1–2 hours. The gastric factor in satiation of thirst seems definitely to be related to distention of the stomach, presumably affecting "pressure receptors". It is not affected appreciably by the type of fluid introduced into the stomach. The absorption and eventual redistribution of fluids in the body presumably would confer permanent satisfaction of thirst after 1–2 hours. The mechanism by which this is accomplished or the time interval required need to be established. The effect of absorption and distribution of fluids in satisfying thirst might be mediated either through osmo or volume receptors, or through effects on the salivary glands. The results of these experiments would indicate that fluids introduced directly into the blood cannot substitute for the gastric factor in the satisfaction of thirst at least for the 1st hour and probably for periods up to 2 hours after ingestion.

Hemorrhage

Another condition that will affect water intake is hemorrhage. A fluid intake of 250 ml for 12 hr preceding hemorrhage was increased to 755 ml for 12 hr following the loss of 470 ml of blood (ref. 127). However, Holmes and Montgomery (ref. 128) observed that following hemorrhage, thirst occurred only when associated with shock.

Heat and Hypohydration

The effect of heat on the water intake in dogs was studied by Flinn (ref. 129). The purpose was to apply the experimental results from dogs to furnace workers employed in the glass industry. In the dogs ad libitum water drinking kept the body temperature down, allowed no change in the alkali reserve, and kept the blood sugar concentration and the blood solids from rising. The dogs were able to maintain their body weights within 3 percent during 4 hr at 50° C while drinking water at 30° C. It was noted that dogs were more severely affected at those high temperatures than the furnace workers.

Dill, Bock, and Edwards (ref. 130) observed the same phenomenon. When water was taken ad libitum by man and dog, during a long walk in the heat, the dog maintained its body weight but the man progressively lost weight. That was an example of involuntary hypohydration in the man. The difference in water intake was attributed to the salt loss in the man. The serum chloride concentration in both the man and dog remained essentially constant. Presumably, enough water was drunk to maintain a constant chloride concentration. Since the man was losing salt in his sweat, he drank less water as time went on.

Dogs exposed to 48° C for 4 hr did not drink enough water to maintain their control body weight (refs. 131 and 132). The drinking pattern varied with the time of exposure. During 2-hr exposures the total water intake was the same whether water was drunk ad libitum during the exposure or taken after the exposure was completed. During a 4-hr exposure, the quantity of water drunk was larger after the exposure compared with ad libitum drinking during the exposure. Two-hour hypohydrations affected primarily the volume of the extracellular compartment while the 4-hr hypohydrations depleted both intracellular and extracellular spaces (ref. 132). This would indicate that the intracellular hypohydration probably

caused the increased water intake after the 4-hr exposure.

Shek (ref. 133) found that the rate of absorption from the small intestine was inversely proportional to the rectal temperature. An increase by 3° C or more considerably reduced the intensity of absorption in all the experiments. The dogs were, on the average, 2.0 to 3.5 percent water depleted during the above experiments. Stickney, Northup, and Van Liere (ref. 134) noted that only severe hyperthermia caused a significant reduction in the motility of the small intestine; strenuous exercise, cold, pain, hypohydration, and moderate hyperthermia were ineffective.

During high-temperature stress there was an increase in urinary potassium through tubular secretion, which might be a compensatory adjustment of the intracellular osmotic equilibrium due to the rapid water loss (refs. 135 and 136). During hypohydration, urinary sodium and chloride, after an initial rise, fell in both concentration and total quantity (ref. 137). After anesthetized dogs were exposed to 49° C for 3 to 4 hr, the glomerular filtration rate and renal plasma flow fell significantly in both the hydrated and hypohydrated conditions. This fall was due to a slight decrease in the mean systemic blood pressure combined with a progressively increasing intrarenal resistance (ref. 138). It would seem that heat exerts its influence independently of the degree of bodily hydration and that the kidney has difficulty in compensating for the changes.

Exercise

Muscular exercise has been shown to inhibit water intake. Two dogs, running on a treadmill for 90 min at 12 km/hr, did not drink enough water to compensate for their weight loss (ref. 139). The same results were observed following running for 90 min at 9 km/hr at 30° to 36° C. However, when the dogs were allowed to drink after a heat exposure without exercise, the time that water was offered significantly influenced the water intake. If water were provided only at the end of the 60- to 120-min heat exposure, the dogs drank water approximately equal to their weight loss. If

water were given only at the end of each 30-min period, the dogs drank about 14 percent more water than their weight loss. If water were allowed ad libitum, the dogs drank about 28 percent more water than their weight loss (ref. 139). Since dogs exposed (1) only to heat overdrank and (2) only to exercise underdrank, a reasonable inference is that exercise is dominant over heat in determining water intake. In men it was also observed that exercise and hypohydration are more effective in inhibiting drinking than is heat (ref. 42).

Gastrointestinal Factors

Another factor that must be considered is the effect of exercise on gastrointestinal functions. Muscular exercise had a marked inhibitory effect on gastric stimulation, whether induced by histamine or by food (ref. 140). The inhibitory condition could be transferred by a blood transfusion from an exercising dog to a resting one. Shek (ref. 141) could detect no change in distilled water absorption after dogs ran 60 to 90 min at 9 to 9.5 km/hr. No absorption of isotonic saline was observed either in the resting state or after muscular work. Crisler et al. (ref. 142) reported, "Anoxemia of grades of 10 percent oxygen or less, in barbitalized dogs, causes inhibition of gastric digestive motility as indicated constantly by a decreased amplitude of contraction and frequently by a fall in tone." Further studies must be made to clarify the relationship between exercise and gastrointestinal functions.

The role of the salivary glands in the thirst mechanism in dogs is controversial. Montgomery (ref. 143) found that after total extirpation of the salivary glands the average daily water intake was not increased. The buccal mucosa remained in a rather moist condition. Gregersen and Cannon (ref. 144) extirpated the salivary glands and tied off the parotid ducts and found an increase in water intake following 1 to 2 hr of panting. Thus a dry mouth was associated with increased drinking while a moist one was not.

Stomach distension reduced the volume and frequency of sham-drinking (ref. 109) and decreased the water intake following intravenous

injections of 20-percent NaCl (ref. 145). If the distention (balloon) was introduced 40 min before the salt injection and then deflated when the salt was injected, drinking was delayed up to 1 hr. The inhibition of drinking did not occur if the stomach was distended for only 5 min. Cocainization of the stomach abolished the inhibition of drinking caused by the stretching of the stomach (distension inhibition) (ref. 146). Hypohydrated dogs transferred four to eight times as much fluid from the stomach to the duodenum during a 10-min observation period (ref. 147). The sensing mechanism for this differential emptying was attributed to the chemo- and osmo-receptors of the stomach.

Food Intake

Fasting can reduce the water intake to 25 percent of normal (refs. 148 and 149), but drinking will gradually increase as the deprivation continues (ref. 150). Dogs drank almost all their 24-hr volume within 2 to 5 hr after feeding, but if water was withheld for several hours following each feeding, the 24-hr intake was much less than when water was allowed ad libitum throughout the postprandial period (ref. 148). The postprandial thirst was, in part, temporary. Provided the diet was held constant, there was a quantitative linear relationship between food and water intakes in 18 dogs over a period of 7 years (ref. 150). When the dietary water content was changed, drinking was readjusted so that the ratio of water to food remained constant.

Recapitulation

The rehydration literature on dogs may now be summarized.

1. Water intake is influenced by food intake. Fasting decreases water intake to about 25 percent of the normal volume, but drinking slowly recovers with time. Postprandial thirst is temporary. Over long periods of time the water-to-food ratio is practically constant.

2. Substances used to increase the blood osmotic pressure can determine the rate and volume of water intake. NaCl injections stimulate drinking immediately, while urea delays the onset. Sorbitol and sucrose act like NaCl; glucose acts like urea. The sodium ion is more important than the chloride in stimulating drinking, but neither ion is the sole regulator of water intake. Water intake is more closely related to the intracellular volume than to the extracellular volume. Hemorrhage stimulates drinking, especially when accompanied by shock.

3. Water passing the pharynx gives temporary satisfaction. A dry mouth increases water intake. Anesthetizing the pharynx and sectioning the nerves of taste and smell has no effect on the quantity of water consumed.

4. Increased pressure in the stomach inhibits water intake. The pressure must be present longer than 5 min. Cocainization of the stomach abolishes the distension inhibition. Vagotomy increases and thoracic sympathectomy decreases the size of the drinks. Total stomach denervation does not alter drinking. Gastric distension is partially or wholly independent of neurohypophyseal lesions.

5. Neurohypophyseal lesions definitely affect water consumption. Ventralanterior hypothalamic lesions cause polydipsia while dorsolateral lesions lead to adipsia. The adipsia is not related to diabetes insipidus. The lesions, if properly made, are specific for water and not food. Depressed drinking is, within limits, proportional to lesion size. With neurohypophyseal lesions, the drinking response is independent of urinary excretion.

6. Thyroid feeding increases water consumption. Procaine has no general effect on drinking. Pitressin delays the onset of drinking and is not a drinking stimulus. Amphetamine inhibits water intake but the inhibition is abolished following prefrontal lobotomy.

7. Muscular exercise depresses water consumption.

8. Individuality plays an important role in drinking. Each animal has its characteristic drinking pattern and drinks about the same amount of water in each draft. The latter is not influenced by environmental temperature, food, total water intake, or small changes in body weight. The daily water consumption is often determined by the number of drinks, not the volume of each draft. Some dogs correct any water imbalance mainly by drinking

while others correct it mainly by excretion. 9. Dogs in very hot surroundings exhibit involuntary hypohydration, probably due, in part, to gastric inhibition. Dogs in warm surroundings often overdrink, while at room temperature they rapidly drink water equal to their weight deficit. Lack of body water, not the time between drinks, starts drinking. Thirst is not always proportional to the severity of hypohydration. Under some conditions of hypohydration the water intake and the urine output may be normal. The kidneys are not *the* mechanism of thirst regulation in the dog.

RATS

The material in this section will be reviewed in the following sequence: normal pattern of water intake in the rat, neuroendocrine factors, electrolyte changes, gastrointestinal influences, heat and hypohydration, hemorrhage, and physiological-psychological parameters involved in drinking, followed by a recapitulation.

Normal Drinking Pattern

Adolph (ref. 151) has described the normal pattern of water intake in the rat:

Clearly the rat takes slightly more than enough water to restore water balance, just as the dog and rabbit do. The chief differences are that the rat requires nearly an hour to ingest this water instead of the few minutes used by those species, and that initial body weight is an insufficient measure of zero load of water.

Involuntary hypohydration has been observed in the rat, partly because the rat characteristically drinks small amounts of water at each draft; it was less in very young rats and greater in adults (ref. 152). In addition, the involuntary hypohydration was controlled to a very small degree by the kind of food available. Adolph and others (ref. 152) have presented a comprehensive theory of water intake in the rat:

Water intake may be separated into four phases:
  a) seeking water . . .
  b) drafting water, which is driven by the urge to drink
  c) stopping the draft at a measured amount, this temporarily counteracting a & b
  d) absorbing and distributing the water to tissues generally and to unknown receptors in particular, whereby the drives for a & b are removed

The stimuli evidently activate a & b. The modulators control c, since they shorten or prolong the drinking period, and its intermittency. The total result in tissues is eventually fed back (d) to neutralize the system which activated a & b. Receptors that activate a & b are often thought to be imbedded in the hypothalamus. Receptors that activate c may mostly be elsewhere and at least in stomach, pharynx, and tongue.

This theory is probably applicable to most other animals, including man. Body weight and skin area were not directly related to water intake. If an indirect relationship was adduced, it appeared to be dependent upon food intake (ref. 153). Water ingestion has also been found, in general, to be tempered to excretory capacities and food intake (ref. 154).

Neuroendocrine Factors

After cutting the olfactory bulbs, the operated rats drank 60 percent more water than control animals. Rats with cut olfactory bulbs reacted to a water deficit primarily by decreasing urine excretion while normal animals did so by increasing water consumption (ref. 155).

Smith and McCann (ref. 156) suggested that the areas in the hypothalamus regulating food and water intake were separable. Lesions of the lateral hypothalamus produced only adipsia in 11 out of 100 rats. The other 89 were both adipsic and aphagic. The specificity of the ventromedial hypothalamic nucleus in controlling only hunger has been questioned. Electric current levels that inhibit eating were generally sufficient to cause rats to stop drinking as well (ref. 157). It was suggested that the most ventromedial stimulation prevented eating by distracting or upsetting the rats. The dependence of drinking upon food intake could be explained by the proximity of the two centers in the hypothalamus.

It has been suggested that the subcommissural organ played an important role as a thirst regulator and had endocrine properties (refs. 158 and 159). Foldvári et al. (ref. 160) examined the influence of the subcommissural organ (SCO) on electrolyte balance and concluded that the SCO was important in regulating salt balance and was a mineralocorticoid activator. Other investigators concluded that the SCO played no role in water metabolism through con-

trol either of thirst or of aldosterone secretion (ref. 161).

Some strains of mice, when treated with estradiol, increased their drinking and excretion of fluids. There was also a retention of water (ref. 162). Atropine has been used to test the dry mouth theory of thirst (ref. 83). Contrary to Cannon's results on man, more recent evidence indicated that atropine depresses drinking in rats, and the effect was not dependent upon food intake (ref. 163). Stein (ref. 164) investigated the effect of atropine and scopolamine on eating and drinking and concluded that the depression of eating was a peripheral effect and the depression of drinking was central. While the two anticholinergic drugs markedly reduced water intake, their methyl analogs did not.

Atropine, administered intramuscularly, pilocarpine, doryl, and posterior pituitary extracts inhibited the large turnovers of water that rats were induced to drink when large amounts of water were mixed with their food. Of the drugs tested, only postpituitary extract suppressed diuresis; the other three seemed to inhibit water ingestion and thirst (ref. 165). After pitressin injections, the voluntary water intake decreased more than urine volume and plasma osmolality was increased significantly over the control group (ref. 166). Thus, the antidiuretic hormone may have a depressing effect on water intake.

Electrolyte Changes

Gamble, Putnam, and McKhann (ref. 167) measured the water requirements for removal of urea and the electrolytes NaCl, potassium chloride, and potassium bicarbonate. They concluded that the water requirement for each of the three salts was nearly the same, but the quantity of water necessary for removing equiosmolar amounts of urea was much less. After slow infusions or rapid injections of varying amounts of hypertonic sodium sulfate, NaCl, sucrose, or urea, the amounts of water consumed by nephrectomized rats were the same (ref. 168). In addition, the drinking threshold was independent of the rate of infusion. The threshold of drinking of nephrectomized rats infused with hypertonic Na_2SO_4 and NaCl was approxi-

mately a 2-percent increase in osmotic pressure (ref. 168); sucrose was 2.4 percent and urea was 5.6 percent. The threshold of normal rats to hypertonic NaCl was a 1.6-percent increase in osmotic pressure. Here again we see that the kind of osmol is important in water intake.

The method of producing hypohydration determines the pattern of drinking. Subcutaneous injections of NaCl delayed the onset of drinking by 8.8 min while drinking commenced immediately following deprivation and continued for 15 min (ref. 169).

The electrical conductivity of brain tissue is related to the degree of thirst in rats. The concentration of electrolyte by itself did not predict water intake even though there was a close relationship between the two variables (ref. 170).

O'Kelly (ref. 171), using the technique of predrink stomach loading, studied the water ingestion in rats water depleted $23\frac{1}{2}$ hr after: (1) varying the volume of preloaded tap water; (2) using fixed preloaded water volumes of varying NaCl concentrations; and (3) allowing rats voluntarily to drink NaCl solutions of varying concentrations. In the first experiment, voluntary intake was decreased proportionally to the volume of the preload; the total intake, preload plus voluntary, increased proportionally to the preload volume. The results of the second experiment indicated that preloading 0.50- to 0.75-percent saline solutions significantly increased water intake above the drinking that followed preloading with water or 0.25-percent saline. Saline solutions of 1.00 to 3.00 percent produced even greater voluntary water intakes. When the rats drank various salt solutions ad libitum (experiment 3), any concentration from 0.25 to 1.00 percent produced an increase in drinking over rats drinking tap water; however, no significant differences in intake were observed between the 0.50- and 1.00-percent solutions. Both of them were drunk in significantly greater quantities than either 0.25-percent saline or tap water. Taste, as well as an absorption factor, was implicated in determining water ingestion. Solutions of NaCl greater than 1 percent were consumed in decreasing amounts. When these hypertonic solutions were placed directly into the digestive

tract they stimulated drinking. Thus, the animal was protected against hypohydration because hypertonic fluids in the intestine stimulated drinking while drinking was inhibited by hypertonic fluids in the mouth (ref. 171).

Gastrointestinal Influences

As in the dog, gastric factors play an important role in the drinking response in rats. Rats, preloaded with water following 23-hour food and water deprivation, showed drinking patterns different from rats which had experienced only water deprivation. Any preload of water greater than half the maximal voluntary consumption inhibited water intake; preloaded water tended to inhibit eating, the effect being more pronounced at the end of the test hour than at the beginning. There was a differential inhibition of the preloaded water on food and water consumption during the first 15 min of the test hour when hydration was less likely to be an important factor (ref. 172). Water by mouth reduced thirst to a greater degree than the same amount of water injected directly into the stomach, pointing up the pharyngeal satiating effect (ref. 173).

Taste, and other sensory mechanisms in the mouth, water depletion produced by the osmotic effects of hypertonic solutions in the stomach, and gastric distension were re-emphasized as having an important influence on drinking (ref. 174). However, recent evidence would tend to de-emphasize the importance of the pharyngeal effect. During periods of direct intragastric self-injection (nasal-stomach tube), the daily water intake remained within normal limits (ref. 175). This observation indicated that normal water intake occurred without the consummatory acts of licking and swallowing.

X-irradiation alters the water intake of rats eating normally. Following whole body irradiation (500 r), two periods of polydipsia were observed: The first occurred within 24 hr following exposure. The second commenced after at least 48 hr postirradiation or longer in proportion to the dose received and was associated with recovery and resumption of the normal food intake (ref. 176).

Like that of the dog, the water intake of the rat is closely associated with food consumption (ref. 177). Both drinking during starvation and eating during hypohydration progressively declined below the intake under ad libitum conditions (refs. 178 and 179). Intake of either food or water seemed to be controlled by the deprivation conditions. A reduction in drinking was found to result from the animal's consuming less at a time rather than its consuming less frequently (refs. 178 and 180). The gastric contents of animals fed with or without water was about 49-percent water. Withholding water during eating decreased the appetite, effected a reduction in food consumed, but did not appear to interfere with digestion (ref. 179).

Heat and Hypohydration

Recovery from hypohydration is a gradual process in the rat. The drinking is rapid and continuous for the first few minutes only and it takes over an hour to rehydrate to the control weight. The rat characteristically overhydrates as do the dog and rabbit (ref. 151). Rats drink very little when exposed to very hot environments but often overhydrate in moderately warm temperatures (ref. 154). Finger and Reid (ref. 181) found that it took rats less than 24 hours to recover from a 24-hour hypohydration, but it took them about 6 days to recover from a 72-hour hypohydration.

Water intake showed a sigmoid relationship to privation interval. The relation between number of hours of privation and the body weight loss was linear and negatively accelerated (refs. 182 and 183). According to Stellar and Hill (ref. 180):

Under all conditions, the rat drinks at a constant rate or it does not drink at all. The tongue always laps water at a rate of six to seven times per second, and with each lap, rats get between 0.004 and 0.005 cc of water. Thus, whenever the rat drinks, it drinks at a rate of about 0.03 cc per second.

Hemorrhage

When rats were hemorrhaged to about 45 percent of their blood volume, they drank no more than did control animals during a 3-hr observation period (ref. 184). On the other hand, Fitzsimons (ref. 185) noted that the removal of

about one-third of the total blood volume caused a five-fold increase in water consumption over sham-bled controls. The rats did not go into shock as a result of the hemorrhage. This increased drinking was ascribed to a thirst-like sensation produced by body fluid diminution without an increase in osmotic pressure.

Physiological-Psychological Parameters

Some of the results dealing with psychological factors may be summarized as follows:

1. Reduction of stimulation (a restricted environment) reduced food consumption and water intake. The former fell off about 25 percent and the latter about 13 percent (ref. 186).
2. After eating dry food, rats failed to demonstrate a learned drive based on thirst (ref. 187).
3. Food acts as a reinforcer (reinforces eating behavior) only if a rat has incurred some critical body weight loss, and provided a rat was deprived of water some critical period of time (ref. 188).
4. Thirsty rats would lick at a stream of air (air-drinking) and this acted as a reward for thirsty rats but not satiated ones. Air-drinking caused excessive saliva losses, reduced subsequent water consumption, and reduced the rate of bar pressing in order to get water (ref. 189).

Recapitulation

A summary of the factors (other than physiological-psychological) influencing drinking in rats is as follows:

1. Under comparable circumstances, the rat takes about 10 times as long to recover from a water deficit as does a rabbit or dog. Older rats exhibit a greater lag in drinking than very young rats. Water intake is controlled by the frequency of drinking rather than by varying the volume during each drink. Thus, rats drink at a constant rate or not at all. The rate of drinking is about 0.03 ml/min. Body weight and skin area do not seem to be directly related to voluntary water intake.
2. Following water deprivation, the rat overhydrates slightly in a normal or moderately warm environment while very hot surroundings significantly inhibit drinking.
3. Gastrointestinal factors and hypohydration are closely related to drinking responses. Water by mouth causes a greater reduction in drinking than an equal amount introduced directly into the stomach. Preloaded water, greater than one-half the ad libitum intake, inhibits eating and drinking. Drinking during starvation and eating during hypohydration are both reduced when compared to normal conditions. Following water depletion preloaded water inhibits drinking; preloaded saline (0.25 to 1.00 percent) produces an increase in water consumption in proportion to the salt concentration. Water intake is related logarithmically to the privation interval; body weight loss is related linearly to the privation interval. Following X-irradiation, rats show two periods of polydipsia, one at 24 hours and the second after 48 hours.
4. Stimulation of the hypothalamic ventromedial nucleus upsets drinking as well as eating behavior. Cutting the olfactory bulbs increases water consumption about 60 percent. Olfactomized rats react to hypohydration by reducing urine loss while normal rats react by increasing their water consumption. The influences of the subcommissural organ on drinking are controversial and not well defined.
5. Atropine can inhibit water intake independent of food intake. Atropine and scopolamine are thought to inhibit drinking centrally and eating peripherally. Their methyl analogs do not show this inhibitory function. Antidiuretic hormone will inhibit drinking as well as diuresis.
6. The effects of hemorrhage are controversial. In one case, drinking after loss of one-half the blood volume was no different than the controls; in another, water intake after loss of one-third the blood volume was five times greater than the control animals.
7. Subcutaneous injections of sodium chloride delay the onset of drinking while hypohydration does not. The brain electrolyte concentration per se will not lead to accurate prediction of water consumption.

OTHER ANIMALS

Observations pertinent to the factors controlling water intake will now be summarized.

1. Following water privation, the rabbit recovered its body weight loss a few minutes after taking water (ref. 151).

2. Fourteen gastric stretch receptors were identified in the pyloric region in cats. The receptors, connected to vagal afferent fibers, slowly reacted to increasing distensions and showed spontaneous activity (ref. 190).

3. The mourning dove can tolerate a water loss equal to 24 percent of its body weight. Once drinking has begun, it makes up this deficit in 10 to 15 min (ref. 17).

4. The trauma connected with polydipsic-producing lesions of the hen's hypothalamus caused an initial decrease in water consumption before the polydipsia began (ref. 191).

5. Emotional factors and hydration in goats (5 l. of water by stomach tube) increased the stimulus threshold for drinking with permanent hypothalamic electrodes implanted in the "drinking center." The goats preferred water at 30° C to water at 12° C (ref. 192).

6. Warming the preoptic area and the rostral hypothalamus in hungry goats inhibited eating and also induced them to drink large quantities of water (ref. 193).

7. Chronic cooling of the preoptic area in goats inhibited water consumption while causing little alteration of food consumption (ref. 194).

8. Placing air, sea water, or plain water in the stomach inhibited the drinking of an equivalent amount of water in the rat, hamster, guinea pig, and adult rabbit; the dog and young rabbit need larger quantities of water or air in the stomach to signal them to stop drinking (ref. 195).

9. In rabbits, studied for 6 months, there was a quantitative linear relationship between food and water intakes. The intake of both food and water decreased with increasing age, water at a slightly greater rate than food. The sudden removal of food led to polydipsia and polyuria; saline ingestion abolished the polydipsia, equimolar solutions of potassium chloride did not. Young female rabbits showed polydipsia to sudden food deprivation; during maturity the polydipsia declined; in old age the polydipsia returned. Castration of the females abolished this cyclic response (ref. 196).

10. In rabbits, D_2O exchange is slowest in the stomach, faster in the small intestine, and fastest in the large intestine (ref. 197).

11. When water was placed in the small intestine of rats, cats, and rabbits, a significant increase in the plasma hemoglobin concentration occurred which suggested that intravascular hemolysis resulted during water absorption (ref. 198).

12. Hypertonic saline solutions injected intravenously in cats resulted in increased electrical activity in the floor of the fourth ventricle at the level of the obex. This area may be a central site of osmoreception (refs. 199 and 200).

13. The camel can tolerate water losses of 30 percent of its body weight, and continues to eat until the hypohydration becomes severe. The camel can drink enough water in 10 to 15 min for complete rehydration (ref. 201). Riley (ref. 202) related an interesting account of drinking in camels:

It was here that I had an opportunity of ascertaining the quantity of water which a camel could drink at one draught. We filled a large goat skin fifteen times, containing at least four gallons, and every drop of this water was swallowed down by our largest camel, amounting to the enormous quantity of sixty gallons, or two barrels . . . . This camel was a very large and old one, about nine feet high, stout in proportion, and had not drunk any water for twenty days, as I was informed by Sidi Hamet; but the other camels did not drink as much in proportion.

14. Following 4 days of water deprivation, oxen drank up to 65 l. of water in 4 min (ref. 203).

SUMMARY AND CONCLUSIONS

Involuntary hypohydration was defined as a depression in the rate of water intake following water loss in animals and in man. While most animals rehydrate fairly rapidly, the rat and man do not. Concerning the speed of voluntary rehydration, the rat is about midway between man and the dog, cat, rabbit, burro, and camel. The pertinent question to be answered is why man takes up to 72 hr or longer to regain a water deficit of 6 percent of his body weight when the other animals can do it in 1 hr or less.

In man, the water intake is not proportional to the total volume of body water. Regardless of the level of the water deficit and whether the water was lost by deprivation or by sweating, man regains the lost water at a constant rate (ref. 42). There is no gulping of water, as in animals, until the deficit is regained. Instead, man will drink rapidly about 1 l. of water and then stop. If water is forced beyond this point,

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vomiting will usually ensue. Prolonged forcing of salt-free water may cause water intoxication which the vomiting would help to prevent.

There are many factors that influence drinking such as: the volume of body water, osmotic concentration, gastrointestinal absorption rates and stretch receptors, food and salt ingestion, starvation, environmental temperature and humidity, physical exercise, and psychological and social parameters. It is clear that attempts to explain drinking on the basis of a single variable, that is, the osmotic concentration or the concept of volume of fluid, have not proved too successful because both factors are operating simultaneously and are mutually interdependent.

The task now is to uncover the relationships between the many variables applicable to water metabolism and to determine how they relate to the time factors in drinking.

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